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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/715,229	11/17/2003	Tariq M. Rana	UMY-041	5733

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LAHIVE & COCKFIELD
28 STATE STREET
BOSTON, MA 02109

EXAMINER

CHONG, KIMBERLY

ART UNIT	PAPER NUMBER
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1635

DATE MAILED: 08/15/2006

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.		Applicant(s)	
	10/715,229		RANA, TARIQ M.	
	Examiner		Art Unit	
	Kimberly Chong		1635	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

- 1) ☒ Responsive to communication(s) filed on 15 May 2006.
- 2a) ☒ This action is FINAL. 2b) ☐ This action is non-final.
- 3) ☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

- 4) ☒ Claim(s) 1-34 is/are pending in the application.
- 4a) Of the above claim(s) 18-34 is/are withdrawn from consideration.
- 5) ☐ Claim(s) _____ is/are allowed.
- 6) ☒ Claim(s) 1-17 is/are rejected.
- 7) ☐ Claim(s) _____ is/are objected to.
- 8) ☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

- 9) ☐ The specification is objected to by the Examiner.
- 10) ☐ The drawing(s) filed on _____ is/are: a) ☐ accepted or b) ☐ objected to by the Examiner.
 Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).
 Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).
- 11) ☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

- 12) ☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).
- a) ☐ All b) ☐ Some * c) ☐ None of:
1. ☐ Certified copies of the priority documents have been received.
2. ☐ Certified copies of the priority documents have been received in Application No. _____.
3. ☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

- | | |
|--|---|
| 1) <input type="checkbox"/> Notice of References Cited (PTO-892) | 4) <input type="checkbox"/> Interview Summary (PTO-413) |
| 2) <input type="checkbox"/> Notice of Draftsperson's Patent Drawing Review (PTO-948) | Paper No(s)/Mail Date. _____ |
| 3) <input checked="" type="checkbox"/> Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) | 5) <input type="checkbox"/> Notice of Informal Patent Application (PTO-152) |
| Paper No(s)/Mail Date <u>1/17/2006</u> . | 6) <input type="checkbox"/> Other: _____ |

DETAILED ACTION

Status of Application/Amendment/Claims

Applicant's response filed 5/15/2006 has been considered. Rejections and/or objections not reiterated from the previous office action mailed 11/15/2005 are hereby withdrawn. The following rejections and/or objections are either newly applied or are reiterated and are the only rejections and/or objections presently applied to the instant application.

The text of those sections of Title 35, U.S. Code not included in this action can be found in a prior Office action.

With entry of the amendment filed on 05/15/2006, claims 1-34 are pending in the application.

Response to Applicant's Arguments

Re: Claim Rejections - 35 USC § 112

The rejection of record for claims 3-17 under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement is maintained. Applicant's arguments are considered but are not persuasive.

Applicant argues the specification "provides ample teaching as to the sequence and structure of siRNAs which can be used for allele-specific cleavage of an mRNA." Applicant further argue the specification "teach numerous examples of diseases caused by dominant, gain-of-function gene mutations, including Alzheimer's disease, Huntington's disease, Parkinson's disease and ALS" and argues the sequences of the mutant alleles responsible for the above mentioned diseases is known and easily obtainable at the time of filing. Further

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Applicants argue the specification provides guidance for selecting the sequences of siRNA molecules to target a particular mutant allele.

The specification does provide general guidelines for generating siRNAs which may be used in allele-specific cleavage of an mRNA encoded by a mutant allele, however these guidelines do not address the particulars of the siRNA design and selection process required for obtaining siRNA against any mutant allele such that one of ordinary skill in the art reading the specification at the time of filing could envision any siRNA targeted to an vast number of mutant alleles responsible for gain-of-function diseases. Although the specification adequately describes siRNA compounds targeted to cells expressing reporters GFP and RFP (see Examples 1-3), by fully setting forth their sequence and function, and by describing the materials and methods needed to measure their activity, adequate written description does not exist for the virtually unlimited number of other siRNA in the claimed genus that target any mutant allele from any specie.

Applicants further argue that the selection of the coding sequences for the instantly claimed siRNAs can be determined using a BLAST search to ensure they did not share significant sequence homology with other genes. Applicants point to the requirement for written description is defined by the Federal Circuit in *Capon v. Eshhar*, 418 F.3d 1349 1357, who state that the written description may be satisfied "if in the knowledge of the art the disclosed function is sufficiently correlated to a particular, known structure" and based on that, it is well known in the field, at the time the application was filed, how to select siRNA molecules targeting a particular gene sequence.

First, one of skill in the art cannot readily extrapolate these general teachings using a BLAST search and specific examples provided in the specification to adequately describing the entire genus of siRNA targeting any mutant gene that would direct cleavage of mRNA encoded by the mutant gene because the art teaches variability within the genus, and the species described do not fairly represent that variability.

It was well known at the time of filing of the instant application that variability exists within the genus. Holen et al. (2002) *Nucleic Acids Res.* 30:1757–1766, for example, report that siRNAs directed against the same target varied widely in their silencing efficiencies (pp. 1759-1760). "...despite the minimal sequence and position differences between these siRNAs, they displayed a wide range of activities" (page 1758). "Our results indicate that susceptible siRNA target sites in some human genes may be rare."(page 1765). "At present, however, the factors determining the differences in siRNA efficiency remain unclear." (page 1761).

The specification does not provide adequate written description of a siRNA targeted to any sequence comprising point mutations and that directs allele-specific cleavage of an mRNA encoded by any mutant allele and the art clearly recognizes that target sequence is a critical parameter and that the design of siRNA is crucial for the success of gene expression inhibition using siRNA. Further, the art does not provide a core structure or motif that would function in directing allele-specific cleavage of any mutant allele and therefore one is left to empirically screen for siRNA compounds of the invention.

Thus, the instantly claimed invention cannot be said to have been adequately described in a way that would convey with reasonable clarity to those skilled in the art that, as of the filing date sought, applicant was in possession of the claimed invention.

Re: Claim Rejections - 35 USC § 102

The rejection of record of claims 1-2, 4-5 and 10-17 under 35 U.S.C. 102(e) as being anticipated by Tuschl et al. (WO 02/44321) is maintained.

Applicant's arguments are considered but are not found persuasive. Applicant argues Tuschl et al. does not teach a siRNA comprising at least one modified base wherein the modified base is capable of enhancing single nucleotide discrimination and is not capable of enhancing binding interactions between the siRNA and mRNA. Applicants further argue the base modifications taught by Tuschl et al. are only for the purpose of increasing stability.

Nowhere in Tuschl et al. does it state these base modifications are only for the purpose of increasing stability. Tuschl et al. teach the siRNA may contain at least one modified analogue, such as a modified base wherein the modified base comprises 5-bromouracil or 5-iodouracil, and the modification may be located at positions that do not interfere with RNAi mediating activity. Therefore, Tuschl et al. anticipates claims 1-2, 4-5 and 10-17 because Tuschl et al. teach a siRNA comprising at least one modified base wherein the modified base comprises 5-bromouracil or 5-iodouracil that are *capable*, absent evidence to the contrary, of enhancing single nucleotide discrimination or enhancing binding interactions between the siRNA and mRNA single nucleotide discrimination.

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The rejection of claim 3 under 35 U.S.C. 102(e) as being anticipated by Xu et al. (US 2004/0192629) is maintained.

Applicant's arguments are acknowledged but are not found persuasive. Applicant argues Xu et al. is not available as a 102(e) reference with regard to the disclosure of a siRNA comprising a modified base. Applicant is correct with regard to claims 4-5 and 9 because the priority applications for Xu et al. do not specifically disclose a siRNA comprising a modified base as listed in claim 4. Accordingly, the rejection of record of claim 4-5 and 9 as being anticipated by Xu et al. (US 2004/0192629) is withdrawn.

However, the rejection of record with regard to claim 3 is maintained. The Xu et al. priority document 60/423,507 teach a siRNA comprising a modified base position opposite a point mutation of the sod1 gene (see Figure 1A). Application 60/423,507 has a filing date of 11/4/2002 and therefore Xu et al. (US 2004/0192629) is available as a reference under 102(e) and anticipates claim 3 of the instant application.

Re: Claim Rejections - 35 USC § 103

The rejection of record of claims 3-5, 7 and 9 under 35 U.S.C. 103(a) as being unpatentable over Xu et al. (US 2004/0192629) in view of Buhr et al. (6,476,205) is maintained.

Applicant arguments are acknowledged but are not found persuasive. Applicant argues Xu et al. is not available as a 102(e) reference with regard to

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the disclosure of a siRNA comprising a modified base because the priority applications do not disclose a modified base.

Xu et al. priority document 60/423,507 teach a siRNA comprising a modified base position opposite a point mutation of the sod1 gene (see Figure 1A). Application 60/423,507 has a filing date of 11/4/2002 and therefore Xu et al. (US 2004/0192629) is available as a reference under 102(e). Xu et al. is not relied upon to teach modified bases comprising a 2,6-diaminopurine. Buhr et al. is relied upon to teach it would be obvious to incorporate a modification such as a 2,6-diaminopurine into an siRNA.

Thus in the absence of evidence to the contrary, the invention as a whole would have been prima facie obvious to one of ordinary skill in the art at the time the invention was made.

THIS ACTION IS MADE FINAL. Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire **THREE MONTHS** from the mailing date of this action. In the event a first reply is filed within **TWO MONTHS** of the mailing date of this final action and the advisory action is not mailed until after the end of the **THREE-MONTH** shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than **SIX MONTHS** from the mailing date of this final action.

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Conclusion

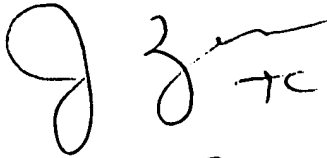
Any inquiry concerning this communication or earlier communications from the examiner should be directed to Kimberly Chong whose telephone number is 571-272-3111. The examiner can normally be reached Monday thru Friday between 7-4 pm.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Peter Paras can be reached at 571-272-4517. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Patent applicants with problems or questions regarding electronic images that can be viewed in the Patent Application Information Retrieval system (PAIR) can now contact the USPTO's Patent Electronic Business Center (Patent EBC) for assistance. Representatives are available to answer your questions daily from 6 am to midnight (EST). The toll free number is (866) 217-9197. When calling please have your application serial or patent number, the type of document you are having an image problem with, the number of pages and the specific nature of the problem. The Patent Electronic Business Center will notify applicants of the resolution of the problem within 5-7 business days. Applicants can also check PAIR to confirm that the problem has been corrected. The USPTO's Patent Electronic Business Center is a complete service center supporting all patent business on the Internet. The USPTO's PAIR system provides Internet-based access to patent application status and history information. It also enables applicants to view the scanned images of their own application file folder(s) as well as general patent information available to the public. For more information about the PAIR system, see <http://pair-direct.uspto.gov>.

For all other customer support, please call the USPTO Call Center (UCC) at 800-786-9199.

Kimberly Chong
Examiner
Art Unit 1635



JANE ZARA, PH.D.
PRIMARY EXAMINER